CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METHYL PARATHION

Chemical Code # 000394, Tolerance # 00121
SB 950 # 043

November 3, 1986
Revised 10/18/89; 1/19/90; 5/23/90; 7/2/90; 12/l/92; 10/31/95; 5/6/96, 11/19/97, 11/25/98, 6/7/02

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect.
Chronic, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, possible adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, possible adverse effect.
Chromosomal aberration:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	No data gap, no adverse effect.

Toxicology one-liners are attached.

All studies identified through document 164 186610 have been examined.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T020608
Revised by: Chernoff, 7/2/90; Kishiyama & Silva,12/l/92; Silva, 10/31/95 & 5/6/96; Aldous (minor editing during revision to current software: no new data, no fundamental changes in content), 9/24/97; Gee, 11/19/97; Silva, 11/25/98; Silva, 6/8/02.

These pages contain summaries only. Individual worksheets may identify additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT
(Chronic/Oncogenicity)

Subchronic, Rat:

099 127031 "A Three Month Feeding Study of Methyl Parathion in Rats," (I. W. Daly & W.E. Rinehart; Project #: 77-2059 (BD-78-9); Bio/dynamics, Inc., East Millstone, NJ; 2/28/80). Methyl parathion (93.65% pure) was fed in diet to Sprague-Dawley CD rats (20/sex/dose) at 0, 2.5, 25 and 75 ppm for 3 months. Systemic NOEL = 2.5 ppm (At 75 ppm, 14 females and 1 male died or were sacrificed moribund during the first 4 weeks on study. All females and 5/20 males showed tremors, emaciation and staining of the anogenital area at 75 ppm. Body weights were decreased and food consumption was increased in both sexes at 75 ppm. Erythrocytes, hemoglobin and hematocrit were decreased and SGOT was increased in females at 75 ppm. Alkaline phosphatase was increased at $\geq$ 25 ppm. BUN was increased while glucose, total protein, albumin and globulin levels were decreased in females at 75 ppm. Males showed decreased globulin, total protein and glucose levels at 75 ppm. Specific gravity in urine was elevated in both sexes at 75 ppm and associated with positive urinary protein determinations of 100 mg/dl or greater in most animals. Male and female organ weights were reduced as follows: testes/ovaries (5%, 22%), heart (8%, 12%), kidneys (10%, 13%) and liver (15%, 26%) at 75 ppm. In addition, relative (organ/brain & organ/body weight) were increased due to decreased terminal body weights. Lesions in the non-glandular mucosa (discolored areas/foci, raised white areas and abrasions, black/brown tar-like gastric contents) occurred in both sexes at 75 ppm. In addition, acute ulcerative gastritis, lymphoid depletion and necrosis (lymph nodes, spleen & thymus), necrosis of the submaxillary salivary glands and hypocellularity of the bone marrow occurred in both sexes at 75 ppm.) Cholinesterase NOEL = 2.5 ppm (RBC and plasma Cholinesterase levels in both sexes were decreased at > 25 ppm. Brain Cholinesterase was decreased in females at > 25 ppm and males at 75 ppm. **Possible adverse effect.** The data are supplemental. M. Silva, 10/17/95.

Combined, rat:

**** 121 - 042, 045 - 050, 098, 148 011168, 034227 - 034232, 126319, 185739** "A Two Year Chronic Feeding Study of Methyl Parathion in Rats," (O'Shaughnessy, D.; Addendum: Reevaluation of Neuropathology Slides from A Two-Year Chronic Feeding Study of Methyl Parathion in Rats (Daly, 1983; BioDynamics Study No. 77-2060); D. O'Shaughnessy Consulting, Inc., Sparta, NJ, 2/8/02). Methyl parathion (93.65% pure) was fed in diet to Sprague-Dawley (CD) rats (60/sex/group) at 0, 0.5, 5.0 and 50 ppm for 25 months (males) or 28 months (females). Systemic NOEL = 5.0 ppm (Decreased body weight gain was observed in both sexes at 50 ppm. Increased food consumption was observed at $\geq$ 5.0 ppm. Clinical signs, including alopecia, ano-genital staining and tremors at 50 ppm and altered gait at $\geq$ 5.0 ppm were observed in females. There was an increased incidence in posterior subcapsular cataracts and retinal degeneration at 50 ppm in both sexes. In addition, females showed decreased HGB and both sexes showed decreased HCT and RBC's at 50 ppm. Histopathologically, both sexes showed peripheral (hindlimb) neuropathy by demyelination of the proximal and distal sciatic nerves at 50 ppm.) ChE NOEL = 5.0 ppm (Significant decreases in plasma and brain cholinesterase were observed at 50 ppm.) **Possible adverse effects:** Significant brain cholinesterase inhibition and peripheral neuropathies occurred at 50 ppm. Retinal degeneration and posterior subscapular cataracts occurred in females at 50 ppm. Originally reviewed as unacceptable but possibly upgradeable (Christopher, 10/7/85), after submission of the requested information has been upgraded to acceptable (Silva, 10/3/95). 148 185739 (D. O'Shaughnessy,

2/8/02) was a re-evaluation of the pathology slides from the original study. The re-read of the slides did not conform with EPA guidelines for a Pathology Working Group (PWG). Report status unchanged. M. Silva, 6/6/02.

NOTE: Record #011168 has been examined several times, with associated changes in acceptability status. The study was initially submitted and found adequate to fill the data gap for a chronic toxicity (Schreider, 3/18/85). Upon submission of additional information (034227-034232), this study was then reviewed as a combined (chronic/oncogenicity) study and considered to be unacceptable but upgradeable (Christopher, 10/7/85). Subsequently, the reports were re-reviewed and the status was still unacceptable, based on animal husbandry problems (see 11/24/92 review sheet by M. Silva for details). After submission of the information requested in the 1992 review, and in consideration of the data in several long-term rat studies, this study has been upgraded to **acceptable** with deficiencies as previously noted (see worksheet by M. Silva, 10/3/95).

EPA ONE-LINER: Oncogenic NOEL>50 ppm (HDT). Neurologic NOEL not defined. Degenerative changes of sciatic nerve in males at high dose level. Thickening of myelin sheaths in high dose females. NOEL (except for neurologic changes) = 0.5 ppm (abnormal gait, slight to moderate decreases in mean hemoglobin, hematocrit and erythrocyte levels in males at 24 months). Effects at 50 ppm include greater incidence of alopecia (particularly in females), bilateral retinal degeneration (females only). CORE grade: minimum (oncogenicity) and supplementary (2 year feeding).

121 - 091, 143 & 144 089191, 185734 & 185735 "A Twelve Month Oral Toxicity Study of Methyl Parathion (E 120) in the Rat Via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects". (I. W. Daly, Bio/dynamics, Inc., Project No. 873208, 1/7/91). Methyl Parathion (purity = 94.6%) was administered in the feed at concentrations of 0 (acetone), 0.5, 2.5, 12.5, or 50.0 ppm to Sprague-Dawley rats (70/sex/group) for at least 12 months. A group scheduled to serve 3 months in recovery was canceled. Systemic NOEL = 2.5 ppm [Decreased body weight gain was observed in both sexes at 50 ppm. Increased food consumption was observed, primarily in females, at $\geq$ 12.5 mg/kg. Clinical signs, including aggressiveness, tremors, scabs, sores, and altered gait (primarily females) were observed at 50 ppm.] Cholinesterase NOEL = 2.5 ppm [Plasma Cholinesterase was inhibited significantly in both sexes at 50 ppm. RBC Cholinesterase was inhibited slightly (no greater than 19.5%) at 50 ppm. Brain Cholinesterase was inhibited significantly at 50 ppm in males and at $\geq$ 12.5 ppm in females.] Neurotoxicity NOEL = 0.5 ppm (there was an increase in peripheral neuropathy at $\geq$ 12.5 ppm in both sexes). In addition, there was an increase in proximal sciatic and tibial/paroneal nerve myelin bubbles at > 2.5 ppm in both sexes. Ophthalmological exams performed at month 12 (retina and optic nerve) failed to show treatment related effects. **NOTE: retinal degeneration and posterior subcapsular cataracts were reported at 50 ppm in an earlier chronic study** (DPR Record #011168), occurring at both 24 and 28 months. Not Acceptable (Not a FIFRA Guideline study). Considered to be supplemental only. Kishiyama & Silva, 11/13/92. Supplemental Data: 063 076585 (protocol for Record 089191). 131 164089 "Re-evaluation of Selected Peripheral (Sciatic and Tibial) Nerve Tissues from a Previously Submitted Chronic Toxicity Study of Methyl Parathion to Rats (Brennecke, L.H., 12/30/96); 143 185734 "Neuropathy Slide Re-Read" (Jortner, B.S., 5/15/01) and 144 185735 "Pathology Re-Evaluation" (O'Shaughnessy, D., 3/21/01) were all re-evaluations of pathology slides from the original study. The re-read of the slides did not conform with EPA guidelines for a Pathology Working Group (PWG). Report status unchanged. M. Silva, 6/6/02**.**

CHRONIC TOXICITY, RAT

051, 052, 063 037188, 037189, 074202, "E 605 - Methyl (Parathion-methyl) Chronic Toxicological Study on Rats (Feeding Experiments Over Two Years)"; (Bayer, 3/31/81). Methyl parathion (94.8%) fed in the diet at 0, *2,* 10 and 50 ppm for 2 years; 50/sex/group; plasma and RBC cholinesterase inhibition indicated adequate dosing; blood chemistry measurements indicated liver and kidney effects at the high dose level, no evidence of oncogenicity effects; NOEL = 2 ppm (cholinesterase

effects); initially reviewed as unacceptable (no diet analysis to verify levels of test article, needed frequency and description of diet preparation, spinal cord and peripheral nerves not examined by histopathology, needed summary tables with actual number of tissues examined, no clinical observations on individual animals); but upgradeable (Remsen, 12/6/85). Record # 074202 contains diet analyses and stability (temperature and conditions not stated), individual clinical observations for a limited number of animals and individual gross autopsy findings. Still UNACCEPTABLE. Now not upgradeable. Gee, 10/16/89.
EPA One liner: Core Grade Supplementary as a chronic study; Core Minimum as an oncogenicity study.

CHRONIC TOXICITY, DOG

** 132 164091 "One Year Oral (Dietary) Toxicity Study of Methyl Parathion in Dogs," (Hatch, R.C., MPI Research, Mattawan, MI; Lab ID #: 668-003; 9/4/98). Methyl Parathion (95.8% pure) was fed in diet to beagle dogs (4/sex/dose) at 0, 0.3, 1.0, 3.0, 3.5 and 4 mg/kg/day at the beginning of the study. After 3 months on study, the 3.0 mg/kg/day group was placed on recovery (given untreated diet) for 30 days and then euthanized and discarded after measuring intraocular pressure. In addition, at this time 2 of the 4.0 mg/kg/day females were moved to the 3.5 mg/kg/day group and 2 of the 3.5 mg/kg/day males were moved to the 4.0 mg/kg/day group. The remaining 4.0 mg/kg/day females (2 dogs) and 3.5 mg/kg/day males (2 dogs) which were not transferred to other groups were euthanized and discarded. Systemic NOEL = 1.0 mg/kg--Females; 1.0 mg/kg--Males (Clinical signs: males at 4.0 mg/kg showed an increase in diarrhea and thinness and a female at 3.5 mg/kg developed clinical signs of epilepsy (this effect may have been idiopathic). Some biochemical parameters (calcium, albumin, total protein) were intermittently decreased in males (6-12 months) at 4.0 mg/kg/day. Females had decreased calcium, total protein, albumin and globulin were observed at 4.0 mg/kg/day (6 months--not measured at 12 months). Relative (adrenal/brain% x 10^3) adrenal weights were increased in a dose-related manner (significant at 4.0 mg/kg/day) after 12 months. Females at 3.5 mg/kg showed significantly decreased, dose-related absolute and relative spleen weights after 12 months. Males (2/4) at 4.0 mg/kg showed mild lymphoid cell depletion in the thymus gland after 12 months. Females showed pituitary gland cysts (mild) at 12 months, primarily at 3.5 mg/kg/day.) ChE NOAEL = 0.3 mg/kg (Males showed significantly inhibited Plasma ChE at 0.3 mg/kg. Plasma and RBC ChE were significantly decreased in both sexes at $\geq$ 1.0 mg/kg throughout the study.) Brain ChE NOEL = 1.0 mg/kg (Males showed significantly decreased caudate nucleus ChE at 4.0 mg/kg.) There were no treatment-related ophthalmological effects, including intraocular pressure and electroretinograms. Acceptable. M. Silva, 11/12/98.

040 011166, "Methyl Parathion: One Year Dog Study", (Pharmacopathics, 8/21/81). Methyl parathion (93.65%) in the diet at 0, 0.03, 0.1 and 0.3 mg/kg/day for one year; 8/sex/group; no effects noted; NOEL = 0.3 mg/kg/day (HDT); UNACCEPTABLE (MTD not achieved, incomplete histology); NOT UPGRADEABLE. Schreider, 3/20/85. In addition, this study is not acceptable since no ophthalmology was performed.
EPA One liner: Core Grade Supplementary.

098 No record number: Response to DPR review of the chronic dog study on methyl parathion. No worksheet, no data. M. Silva, 10/3/95.

070, 085; 090468, "A 13-Week Subchronic Toxicity Study of Methyl Parathion in Dogs Via the Diet Followed by a One-Month Recovery Period", (I.W. Daly, Bio/dynamics, Inc., Project No. 87-3209, 11/20/89). Methyl Parathion, 94.9%, lot #233690479, was administered in the diet to groups of 8 beagle dogs per sex at treatment levels of 0 (diet only), 0.03, 0.30, or 3.0 mg/kg/day for 13 weeks. At the end of the treatment period, 4 dogs per sex per group were terminated, and the remainder were placed on the control diet for a 4 to 6 week recovery period. Ophthalmoscopic, tonometric, and electroretinographic examinations were conducted, and cholinesterase levels measured, prior to, during, and after the treatment period. Plasma, RBC, and brain cholinesterase levels were

consistently decreased at 3.0 mg/kg/day during the treatment period. Intra-ocular pressure was sporadically decreased (mid-dose females and high dose males) only in the recovery period. Systemic NOEL = 0.03 mg/kg/day (decreased intra-ocular pressure); Systemic NOAEL > 3.0 mg/kg/day; Cholinesterase NOEL = 0.3 mg/kg/day. This is ACCEPTABLE AS A SUPPLEMENTAL STUDY, and no adverse effect is indicated (G. Chernoff, 5/22/90).

065 073970, 073974, Supplemental to 090468; draft study design and protocol; no worksheet (Gee, 10/16/89).

SUMMARY: The subchronic study (DPR No. 090468) was submitted for consideration in filling the deficiencies noted in the chronic study (DPR No. 011166), specifically, the concern regarding the lack of an MTD. In the subchronic study, significant plasma, RBC, and brain cholinesterase depression effects were observed at 3.0 mg/kg/day. This dose is 10 times greater than the high dose used in the chronic study (0.3 mg/kg/day). DPR now finds there are sufficient data to fill the chronic dog data gap. M. Silva, 5/2/96.

088 095250 "Data Evaluation Record, Methyl Parathion, Subchronic Oral Toxicity Study in Dogs," (Weir, R.J., EPA evaluation of the subchronic dog study, 9/18/90). This information was submitted to show that EPA had waived further requirements for a chronic dog study. M. Silva, 11/24/92.

No record number, pages only: A letter dated 9/11/90, from Cheminova was a request that DPR not make further decisions about methyl parathion in chronic dog studies until the US-EPA review had been received and evaluated. M. Silva, 11/24/92.

114 145815-145818 "Material in Support of Request for Reconsideration of Acceptability of Dog Chronic Toxicity Data," was submitted by Cheminova, Ltd., as a rebuttal document (March 27, 1996). No worksheet. M. Silva, 4/17/96.

118 150561 Twelve page 3-month interim report on a 1-year dog study with methyl parathion in beagle dogs initiated at MPI Research on April 30, 1996. The report, dated October 18, 1996, contains preliminary data on plasma and RBC cholinesterase inhibition and summary and individual data on intraocular pressure. Doses were 0, 0.3, 1.0, 3.0, 3.5 and 4.0 mg/kg. The mid-dose group of 3.0 was taken off treatment after 3 months and fed control diet for a 4 week recovery period. Cholinesterase was significantly inhibited at $\geq$ 1.0 mg/kg. No effect on intraocular pressure was noted up to the 3-month measurement. No worksheet. J. Gee, 11/19/97.

119 153151 Four page summary of results on the 1-year dog study with data for plasma and RBC cholinesterase results for 1, 3 and 6 months. See # 150561 for additional details. No worksheet. J. Gee, 11/19/97.

ONCOGENICITY, RAT

038 049211, "Bioassay of Methyl Parathion for Possible Carcinogenicity (Rats)", (Litton for NCI, 1979). Methyl parathion (94.6%) fed in the diet at 0, 20 and 40 ppm for 102 weeks; 20/sex in control group, 50/sex/treated group; decreased survival in females at high dose level; insufficient information to gauge potential adverse effects; insufficient data to set a NOEL; unacceptable (only two dose levels, no analysis of diet for test article, inadequate number of control animals, no analysis of time to tumor, no measurement of food consumption, no pathology summary, no hematology or blood chemistry), NOT UPGRADEABLE. Schreider, 3/21/85.
EPA 1-liner: Core Grade Supplementary. Not carcinogenic.

ONCOGENICITY, MOUSE

**094 098865, "Methyl Parathion: Study for Chronic Toxicity and Carcinogenicity in B6C3Fl Mice," (R. Eiben, Bayer AG Fachbereich Toxikologie, Study No.: T4027023, May 17, 1991). Methyl parathion (E120 technical grade, purity = 95.5%) was administered in the feed at concentrations of 0 (peanut oil), 1, 7, or 50 ppm to 15 or 50 B6C3Fl mice/sex/group for 52 or 104 weeks, respectively. Cholinesterase NOEL = 1 ppm/day based on inhibition of RBC Cholinesterase at $\geq$ 7 ppm and inhibition of plasma and brain Cholinesterase at 50 ppm. Systemic NOEL = 7 ppm based on increased body weights with decreased food consumption and increased liver and kidney weights in both sexes at 50 ppm. A treatment-related oncogenic effect was not observed in this study. Acceptable with no adverse effect. J. Kishiyama & M. Silva, 11/24/92.

038 927589 "Bioassay of Methyl Parathion for Possible Carcinogenicity (Mouse)", (Litton for NCI, 1979). Methyl parathion (94.6%) fed in the diet at 0, 62.5 and 125 ppm (changed to 20 and 50 ppm at week 37) for 102 weeks; 20/sex in control group, 50/sex/treated group, B6C3Fl mice; no adverse effects reported; NOEL cannot be established; UNACCEPTABLE (only two dose levels, no analysis of diet for test article, inadequate number of control animals, no analysis of time to tumor, no pathology summary, no hematology or blood chemistry, no food consumption data), NOT UPGRADEABLE. Schreider, 3/21/85.
EPA 1-liner: Core Grade Supplementary. Not carcinogenic.

086 088521, "Oncogenicity Feeding Study in Mice With E-120", (Bayer Study No. T4027023). Protocol for new study (see Record No. 098865, above). No worksheet (G. Chernoff, 7/2/90).

086 088522, "Pilot Dose-Finding Study for a Carcinogenicity Study in B6C3Fl Mice, Administration in the Feed Over 66 Days", (Eiben, R., Bayer AG, Study No. T5025378, 7/87). Results of a range finding study. No worksheet (G. Chernoff, 7/2/90).

086 088523, "Pilot Dose-Finding Study for a Carcinogenicity Study in B6C3Fl Mice, Administration in the Feed Over 65 Days", (Eiben, R., Bayer AG, Study No. T1025518, 7/87). Results of a range finding study. No worksheet (G. Chernoff, 7/2/90).

REPRODUCTION, RAT

****044 011171**, "Two-Generation Reproductive Study of Methyl Parathion in Rats", (Bio/dynamics, Report No. BD-80-139, 7/18/82). Methyl parathion, 93.6% pure, was given in the diet to Sprague-Dawley CD rats (15 males & 30 females/group) at 0 (acetone = vehicle), 0.5, 5.0 and 25 ppm for two generations (one litter/generation). Maternal NOEL = 5 ppm (marginal decrease in weight gain at the end of lactation); Maternal NOAEL > 25 ppm; Reproductive NOEL and NOAEL = 5 ppm (decreased pup survivability). Formerly reviewed as unacceptable (Schreider, 3/18/85) for no justification of dose levels, no characterization of test article, no litter standardization, and incomplete histopathology. The study was upgraded to ACCEPTABLE (M. Silva, 1/19/90) based on an EPA Memorandum resulting in a re-review of the study. Another reevaluation of the study, prompted by the rebuttal in Record No. 086795, resulted in the decreased pup survivability being identified as a POSSIBLE ADVERSE HEALTH EFFECT (G. Chernoff, 5/21/90).
EPA One liner: Core Grade Minimum.

081 086795, Supplemental to 011171; rebuttal arguments (G. Chernoff, 5/21/90).

053 037190, 037191, "E 605-Methyl (Methyl Parathion) Multigeneration Studies on Rats (Reproduction)", (Bayer, 2/8/82). Methyl parathion (95%) was given in the diet at 0, *2,* 10 and 50 ppm for a three generation study; 10 males/group, 20 females/group. There were no pups surviving at the end of F2 generation in the high dose group; NOEL = 2 ppm; UNACCEPTABLE (needs QA statement and final report revisions, no analysis of diet for test article, food consumption not measured, no clinical observations. presented, incomplete necropsy data, gestation and lactation weights included in weekly female weights), NOT UPGRADEABLE. Parker, 12/5/85.

033 927643, "Methyl Parathion - Monograph Number Seven - Environmental Health Evaluation of California Restricted Insecticides (Toxicological Evaluations)", (P.M. Dolinger Assoc., 1979?, page 51). Summary of 3-generation study using methyl parathion (10 and 30 ppm in the diet) conducted by Woodard Research Corp. Reductions in survival noted for Fla, F1b, and F2a generations at 30 ppm and in the F-3a generation at 10 ppm; stillbirth rates were increased in F1b and F3b generations at 30 ppm; UNACCEPTABLE (no data), NOT UPGRADEABLE.
EPA One liner: Core Grade Supplementary.

SUMMARY: A consistent finding in the three rat reproduction studies on file was a decrease in pup survivability. In two of the studies (#Is 927643 and 037190) where the doses included 0, *2,* 10, 30 and 50 ppm, decreased survivability was observed at 10 ppm. In the third study (#011171) where the doses were 0, 0.5, 5.0, and 25 ppm, survivability was decreased at 25 ppm. Taken together, these data indicate decreased pup survivability is a consistent possible adverse effect with a NOEL = 5 ppm (Chernoff, 5/23/90).

TERATOLOGY, RAT

121 - 162 186607 "A Range-Finding Developmental Neurotoxicity Study of Orally Administered (Gavage) Methyl Parathion in the Rat," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID#: 97530; 2/21/02). Methyl parathion (96.5% pure) was administered by gavage to mated Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (6/dose) at 0 (corn oil), 0.1, 1.0 and 2.0 mg/kg from gestation day 6 to 20. Additional mated females (10/dose) were treated by gavage at 0 (corn oil), 0.1, 1.0 and 2.0 mg/kg from gestation day 6 to lactation day 10 and their offspring were treated by oral gavage at the same dose levels from day 11 to 21 *post partum*. Ten pups/sex/dose were selected on post partum day 21 for cholinesterase determinations. Maternal NOEL = 1.0 mg/kg (One female at 2.0 mg/kg was found dead on lactation day 1. Clinical signs of overt toxicity were observed at 2.0 mg/kg (tremors, salivation, abnormal gait, altered activity, absence of nesting behavior, fur staining at the head & body). Body weight, body weight gain and food consumption were statistically significantly decreased at 2.0 mg/kg throughout gestation. Body weight and body weight gains were statistically significantly decreased at 2.0 mg/kg throughout lactation.) Pup NOEL = 0.1 mg/kg (Pup mortality was increased at 2.0 mg/kg that resulted in a slightly or statistically significantly decreased viability index, survival index and overall lactation index. At 1.0 mg/kg, a litter with only 2 live pups, lost both pups to death before day 14 post *partum*. Prior to pup treatment, pups at 2.0 mg/kg had a higher incidence in: dehyration, thin/weak appearance, cold to touch, skin pallor and empty stomach (indicative of lack of nursing). At 2.0 mg/kg, gavaged pups showed post-dosing tremors, salivation, limited usage of hindlimbs or lying on their side after treatment and decreased activity. At 1.0 mg/kg, gavaged pups showed tremors post-dosing, decreased activity and salivation. Some pups at $\geq$ 1.0 mg/kg showed eye abnormalities (damaged, enlarged, hemorrhaged, missing, opacity, shrunken). Both sexes of pups had statistically significantly decreased body weights throughout the *post partum* period at 2.0 mg/kg.)

ChE NOEL = 0.1 mg/kg (Plasma, RBC and brain ChE were statistically significantly decreased at ≥ 1.0 mg/kg in dams and F1 pups.) Possible adverse effects (increased mortality, eye histopathology and ChE inhibition). Not a FIFRA guideline study. M. Silva, 5/21/02

** 121 - 164 186610 "A Developmental Neurotoxicity Study of Orally Administered Methyl Parathion in the Rat," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID#: 97574; 3/1/02). Methyl parathion (96.8% pure) was administered by gavage to mated Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (32/dose) at 0 (corn oil), 0.03, 0.3 and 0.6 mg/kg from gestation day 6 to lactation day 10 and their offspring were treated by oral gavage at the same dose levels from day 11 to 21 *post partum*. Pups were allowed to grow to adulthood, then were tested for behavioral/activity/neurotoxicity effects at 60 days, then terminated at 70 days of age. Maternal NOEL = 0.3 mg/kg (F0 generation had increased salivation at 0.6 mg/kg.) Pup NOEL = 0.3 mg/kg (F1 pups at 0.6 mg/kg showed tremors and salivation post dosing.) Untreated F1 adult NOEL > 0.6 mg/kg (Effects observed in F1 pups/weanlings were not observed in adults when tested at 60 days of age or at termination (70 days).) Cholinesterase activity was not measured. There were no treatment-related differences in brain measurements, observational battery or motor activity. No adverse effect. Acceptable. M. Silva, 5/24/02

121 - 163 186608 "A Study of the Effects of Orally Administered Methyl Parathion on Cholinesterase Levels in Adult, Juvenile and Neonatal Rats," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID#: 97558; 2/26/02). Phase I: Methyl parathion (96.8% pure) was administered by gavage to mated Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (20/dose) at 0 (corn oil), 0.03, 0.3 and 0.6 mg/kg from gestation day 6 to 20 or they were treated from gd 6 to lactation day 10 and their pups were treated from day 11 to 21 *post partum*. Cholinesterase activity was measured from blood (plasma, RBC) and brain of mated females on gd 20, fetuses/pups on gd 20 and days 4, 21 and 60 *post partum*. Phase II: Neonatal Sprague-Dawley rats (8/sex/dose) from untreated dams were gavaged with methyl parathion at 0, 0.03, 0.11, 0.3, and 1.0 mg/kg on day 11 *post partum* (1 day only). Blood and brain ChE were assessed on day 11 *post partum*. Phase III: Young adult rats (49-50 days of age,16/sex/dose) were gavaged with methyl parathion at 0, 0.03, 0.3 and 0.6 mg/kg for 1 or 11 consecutive days. ChE was measured in blood and brain on day 1 (1st dosing day), 11 (last dosing day) and day 60 *post partum* (day 60 was also day of termination). Systemic Maternal NOEL > 0.6 mg/kg (There were no treatment-related effects due to treatment.) Developmental NOEL > 0.6 mg/kg (There were no treatment-related effects due to treatment.) ChE NOEL = 0.03 mg/kg (Plasma ChE at 0.6 mg/kg and RBC and brain at ≥ 0.3 mg/kg were statistically significantly decreased. Fetuses (plasma in females & RBC males) had statistically significantly decreased ChE activity at 0.6 mg/kg. Pups of both sexes at > 0.3 mg/kg had statistically significantly decreased plasma, RBC and brain ChE (day 21 post partum (11 doses). Both sexes of pups (day 11 post partum, 1 dose only) had statistically significantly decreased plasma and brain ChE at ≥ 0.3 mg/kg. Male pups had inhibited RBC ChE at 0.6 mg/kg and females at ≥ 0.3 mg/kg. Young adult males had statistically significantly inhibited plasma and RBC ChE at > 0.3 mg/kg, while females had inhibited plasma and brain ChE at 0.6 mg/kg and RBC ChE at > 0.3 mg/kg after 11 consecutive doses.). Possible adverse effect indicated for ChE inhibition. The data are supplemental. M. Silva, 5/31/02.

****068 085036,** "Embryotoxicity (Including Teratogenicity) Study with E120 TECHNICAL (Common Name: PARATHION-METHYL) in the Rat" (Research and Consulting Company AG, RCC 083553, 12/31/87). Technical methyl parathion, batch 230 606 003, 97% pure in 0.5% aqueous Cremophor EL was administered by oral intubation to groups of 25 mated Wistar/HAN female rats at 0 (vehicle

control), 0.3, 1.0 and 3.0 mg/kg/day on days 6 through 15 of gestation. An additional 10 females each were added to the 0 and 3.0 mg/kg/day groups for cholinesterase activity measurement. **Possible adverse effects:** Decreased maternal cholinesterase activity, maternal signs of organophosphate toxicity, decreased maternal weight gain, decreased maternal food consumption, fetal developmental delay determined by decreased fetal weight and delayed ossification, and a tendency toward increased resorptions, all at 3.0 mg/kg/day. Maternal NOEL = 1.0 mg/kg/day (signs of organophosphate toxicity, cholinesterase inhibition, decreased food consumption and weight gain). Developmental NOEL = 1.0 mg/kg/day (developmental delay and marginal increase in resorptions). ACCEPTABLE study. G. Chernoff, 10/12/89.

055 037196, "Parathion-Methyl Evaluation For Embryotoxic and Teratogenic Effects on Rats Following Oral Administration", (Bayer, 6/3/77). Methyl parathion (94.4%) by oral gavage at 0, 0.1, 0.3 and 1.0 on days 6-15 of gestation; 20 pregnant females/group; fetal body weight decreased in high dose group; NOEL cannot be determined; UNACCEPTABLE (need analysis of dosing solution; need individual data for body weight, food consumption, necropsy parameters, fetal exams, fetal weights and clinical observations.), POSSIBLY UPGRADEABLE. Parker, 12/4/85.
EPA One liner: Core Grade Supplementary.

031 927582, EPA summary of study identified as record #037196.

033 038392, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Teratogenicity, Mammalian Rat Studies", (Dolinger Assoc. Report, pages 48-49). Summary of journal article by Fish (1966) in which rats were injected i.p. with methyl parathion on day 9 or 15 of gestation; insufficient data for evaluation. Study by Tanimura et al. (1967) suggests that one i.p. injection of methyl parathion at 15 mg/kg on day 12 of gestation reduced fetal weight.
EPA One liner: Core Grade Supplementary.

TERATOLOGY, RABBIT

** 095 111287, "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Methyl Parathion Technical Administered Orally via Stomach Tube to New Zealand White Rabbits", (Alan M. Hoberman, Argus Research Laboratories, Inc., Horsham, PA., Report # 310-007, 11/16/91). Methyl parathion technical (95.7% pure) was administered by gavage to artificially inseminated New Zealand White [Hra:(NZW)SPF] female rabbits (19 or 20/group) on gestation days 6 through 18 at 0 (corn oil), 0.3, 3.0, and 9.0 mg/kg/day. Maternal cholinesterase NOEL < 0.3 mg/kg/day (Significant RBC Cholinesterase inhibition occurred at $\geq$ 3.0 mg/kg/day. A significant decrease in plasma Cholinesterase occurred at 9.0 mg/kg/day. Maternal Systemic NOEL: There were no significant maternal effects at any dose. Developmental NOEL = 3.0 mg/kg/day (There was an increased incidence in thickened areas of ossification in the ribs at 9.0 mg/kg/day). **Acceptable, with no adverse effects**. (H. Green & M. Silva, 11/6/92)

055 037197, "Parathion-methyl (Folidol M Active Ingredient) Study for Embryotoxic Effects on Rabbits After Oral Administration", (Renhof, M., Bayer AG Institute of Toxicology, Report No. 12907, 9/4/84). Methyl parathion, 95.7% pure in 0.5% aqueous Cremophor EL emulsion vehicle was administered by oral gavage to groups of 12-15 pregnant Himalayan CHBB:HM rabbits at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6-18 of gestation. No adverse effects were noted. Maternal and Developmental NOEL > 3 mg/kg/day. Initially reviewed as unacceptable but possibly upgradeable

with submission of justification of dosing levels, all the individual animal data, a description of the dosing solution preparation, and an analysis of the dosing solution (Parker, 12/4/85). After review of the supplemental information provided in record nos. 085035 and 088518, the study remains UNACCEPTABLE and is now considered not upgradeable due to the lack of a MTD (G. Chernoff, 6/29/90).
EPA One liner: Core Grade Minimum

068 085035, "Supplement to Methyl Parathion (El2O) Study for Embryonic Effects on Rabbits After Oral Administration", (Bayer, 12/22/87). Supplemental to record no. 037197, consisting of a retrospective range finding study in rabbits at doses of 0, 0.3, 1.0, and 3.0 mg/kg/day. The only notable finding was a minimal reduction in RBC cholinesterase activity on days 14 and 19 in the high dose group (G. Chernoff, 7/2/90).

083 088518, "Additional Information to Methyl Parathion Study for Embryotoxic Effects on Rabbits After Oral Administration", (Renhof, M., Bayer AG, Report No. 12907, 12/22/87). Supplemental to record no. 037197, consisting of a dose justification based on a rat teratology study, individual animal data, test compound analysis, and an abbreviated study protocol (G. Chernoff, 7/2/90).

NOTE: Justification for the dose selection used in the rabbit teratology study (DPR Record No. 037197) has been provided in two separate documents. In the first (DPR Record No. 085035), the results of a retrospective range-finding study were presented. The only finding indicative of an MTD was a marginal decrease in RBC cholinesterase levels at 3.0 mg/kg/day, the highest dose tested. Plasma and brain cholinesterase levels were unaffected by the treatment, as were appearance, behavior, weight gain, autopsy findings, and maternal deaths. The second justification (DPR Record No. 088518), was based on the results of an unacceptable rat teratology study (DPR Record No. 037196), in which a maternal MTD was not clearly established. These data for the rat study are considered inadequate, and inappropriate for dose justification in the rabbit study. Since the demonstration of a clear MTD was not achieved in either the original rabbit teratology study, or in the retrospective range finding study, this information is not sufficient to fill the data gap. DPR Record No. 111287 (Argus Research Laboratories, 11/16/91), however, is an acceptable rabbit teratology study and therefore, the data gap is filled. (M. Silva, 12/l/92).

TERATOLOGY, MOUSE

033 038392, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Teratogenicity, Mammalian Mouse Studies", (Dolinger Assoc. Report, page 49). Summary of journal article by Tanimura et al. (1967) in which mice were injected once i.p. with 20 or 60 mg/kg on day 10 of gestation; in high dose group 13 of 112 fetuses had cleft palate, fetal deaths elevated at the high dose level.
EPA One liner: Core Grade Supplementary.

GENE MUTATION

054 037192, "E120 Parathion-Methyl Salmonella/Microsome Test to Evaluate for Point Mutations (Salmonella Typhimurium)", (Bayer, 8/l/80). Methyl parathion (94.5%) tested at 0, 20, 100, 500, 2500, or 12,500 ug/plate +/- S9 with Salmonella strains TA 1535, TA 1537, TA 98 and TA 100; positive response with TA 1535 with S9 and TA 100 with and without S9; confirmed in repeat experiment; UNACCEPTABLE (no individual plate counts, no controls for -S9 series, unclear description of

bacteriostatic activity, incomplete description of methodology), POSSIBLY UPGRADEABLE. Remsen, 12/6/85.

****054 037193,** "E120 Parathion-Methyl Folidol M Active Ingredient Salmonella/Microsome Test to Evaluate for Point Mutations (Salmonella Typhimurium)", (Bayer, 8/l/80). Methyl parathion (96.1%) tested at 0, 20, 100, 500, 2500 or 12500 ug/plate +/- S9 on Salmonella strains TA 1535, TA 1537, TA 98 and TA 100; positive response in TA 100 and probably TA 98; confirmed with repeat experiments; ACCEPTABLE. See also 37192. Remsen, 12/6/85.

033 038391, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Mutagenicity Microbial Studies", (Dolinger Report, pages 47-48). Summary of several journal articles on the potential genotoxic activity of methyl parathion; insufficient information to evaluate; weakly mutagenic to E. coli at 0.1 M, positive results for mutagenicity in four microbial systems were reported, references were also made to studies with bacterial systems in which methyl parathion did not increase mutation frequency (Schreider, 2/21/85).

CHROMOSOME EFFECTS

054 037194 “E120 Parathion-Methyl Folidol M - Active Ingredient Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect", (Bayer, 3/29/82). Methyl parathion (95.6%) tested in mouse micronucleus assay at 0, 10 or 20 mg/kg by oral gavage given twice at 24-hour interval; 5/sex/group; animals sacrificed after 6 hrs; 1000 PCE's evaluated; no increase noted, but positive control effective; UNACCEPTABLE (only a 6 hr sampling time, only 2 dose levels with no evidence of toxicity - dose selection based on a pilot study where 2 x 10 mg/kg caused "somnolence"), NOT UPGRADEABLE. Remsen, 12/6/85.

**054, 064 037195, 074209-212, "E 120 Parathion Methyl - Dominant Lethal Test on the Male Mouse to Evaluate for Mutagenic Effect", (Bayer AG, 6/7/84). Methyl parathion (95.7%) tested at 0 or 10 mg/kg by oral gavage in mouse dominant-lethal assay; 46 males/group; mated 1:1 for 12 X 4 days; no adverse effect reported; initially reviewed as unacceptable (no positive controls included and no historical controls). Remsen, 12/6/85. Submission of document 121-064 containing three positive control studies with Endoxan in the same strain of mice and a compilation of historical control data in females over a period of years upgrades the study to ACCEPTABLE. Gee, 10/16/89.

031 927582, "Initial Scientific and Microeconomic Review of Parathion: Subpart II. B. Pharmacology and Toxicology", (EPA 540/1-75-001). Summary of a journal article. Single dose of methyl parathion tested on guinea pigs for testicular chromosome aberration. Although potential adverse effect on chromosome abnormalities was indicated, data are inadequate for evaluation. Remsen, 12/6/85.

033 038391, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Mutagenicity Microbial - Studies", (Dolinger Report, page 48). Summary of a journal article by Huang (1973) in which the effect of i.p.-injected methyl parathion on mouse chromosomes was examined; no aberrations were noted in bone marrow chromosomes in a group treated with 20 mg/kg. Remsen, 12/6/85.

DNA DAMAGE

** 067 075728, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes - Methyl Parathion", (Microbiologica1 Associates, 6/22/89). Methyl parathion, lot 95IA-84, no purity stated; tested with primary rat hepatocytes from Fischer 344 male rat(s) at 0 (ethanol and medium), 0.0003, 0.001, 0.003, 0.01, 0.02 and 0.03) : l/ml of medium; tritiated thymidine incorporation over 18 - 20 hour incubation by autoradiography; scored 50 nuclei per each of three slides; 0.03 : l/ml was too toxic to score; no evidence of induction of unscheduled DNA synthesis; ACCEPTABLE. Gee, 10/16/89.

NEUROTOXICITY

** 084 088519, "Methyl Parathion: An Acute Delayed Neurotoxicity Study in the Laying Hen (Gallus gallus domesticus)", (Beavers, J.B., J. Foster, B.Y. Cockrell and M.J. Jaber, Wildlife International Ltd., Project No. 232-111, May 1, 1990). Methyl parathion technical without xylene, 95.8%, Batch #95-lA-57, was administered to 16 adult hens at an initial dose of 250 mg/kg/day (16% above the LD50) with atropine, followed by a second dose of 215 mg/kg/day on day 21. Six hens died within a few days of the initial dosing, and two died within a few days of the second dosing. There were no deaths reported in the negative (corn oil vehicle) control, or the positive TOCP (600 mg/kg) control. Based on the absence of persistent clinical signs, ataxia, or remarkable histopathological findings, there is no evidence to suggest that methyl parathion causes acute delayed neurotoxicity within the experimental conditions of this study. The study is ACCEPTABLE, and no adverse health effect is noted (G. Chernoff, 6/29/90).

103 129644 This document is an adverse health disclosure for an acute neurotoxicity study with methyl parathion in rats. No worksheet. M. Silva, 10/10/95.

**** 129 164087** "Acute Neurotoxicity Study of Methyl Parathion in Rats," (Minnema, D.J., Hazleton Washington, Inc., Vienna, Virginia; Lab. Project ID #: HWA 2688-102; 5/31/94). Methyl Parathion technical (93.1% pure) was administered in a single gavage dose to Sprague-Dawley Crl:CD® BR rats at 0, 0.025, 7.5, 10.0 (males only) and 15.0 (females only) mg/kg. A Functional Operational Battery (FOB) and Locomotor Activity (LMA) were conducted at pre-test and 1.5 hours (time of peak effect), 1 and 2 weeks post-dosing (10/sex/dose). Assessments of plasma, RBC and regional brain cholinesterase were performed at pre-test, 1.5 hours post-dose (all dose groups) and at 2 weeks (control and high dose only). Neurotoxicity NOEL = 0.025 mg/kg (There were increased clinical observations and neurobehavioral effects observed in both sexes at $\geq$ 7.5 mg/kg. Males at $\geq$ 7.5 mg/kg and females at 15.0 mg/kg showed increased incidence and severity of demyelination. Cholinesterase NOEL = 0.025 mg/kg (There was significantly decreased plasma, RBC and brain ChE observed at $\geq$ 7.5 mg/kg in both sexes. At day 14, effects continued at the high dose (low and mid-doses were not assessed.)) Possible adverse effect (increased demyelination, neurobehavioral effects and significantly decreased ChE). Acceptable. M. Silva, 11/19/98.

**** 130 164088** "Subchronic Neurotoxicity Study of Dietary Methyl Parathion in Rats," (Minnema, D.J.; Hazleton Washington, Inc. (HWA), Vienna, VA; Lab Project ID #: HWA 2688-103; 12/19/94). Methyl parathion technical (93.1% pure) was fed in diet to Sprague-Dawley Crl:CD®BR rats (10/sex) at 0, 0.5, 5 and 50 ppm for 13 weeks. Additional animals from the control and high dose animals (5/sex/dose) were designated as recovery (behavioral and cholinesterase) animals (weeks 14 - 17). These animals were also used for a limited FOB testing at weeks 13 & 16 or ChE at week 17. Systemic NOEL = 5.0 ppm (There were increased clinical observations, decreased food consumption and body weights in both sexes at 50 ppm. There were increased effects in the FOB (latency to first step, pupil response, fore-limb and hind-limb grip strength, tremors and other signs)

in both sexes at 50 ppm. Alopecia was observed in both sexes at 50 ppm (1/6).) ChE NOEL = 0.5 ppm (Plasma ChE was significantly decreased in males at 50 ppm and in females at $\geq$ 5.0 ppm. RBC ChE was significantly decreased in both sexes at $\geq$ 5.0 ppm. Regional brain ChE was significantly decreased in males at $\geq$ 5.0 ppm and in females at 50 ppm.) No histopathological findings, including degenerative lesions, were reported. Possible adverse effect: Significant decrease in RBC and brain ChE, which, in some cases, did not return completely to control values after the recovery period. Acceptable. M. Silva, 11/25/98.

125 164083 "Comments from Cheminova Agro A/S on California Department of Pesticide Regulation's Evaluation of Methyl Parathion as a Toxic Air Contaminant," (Reiss, R., Severn, D.J. and Neal, B.; Cheminova Agro A/S, Lemvig, Denmark; Jellinek, Schwartz & Connolly, Inc., October 20, 1998). This is supplemental information relevant to risk assessment for methyl parathion. No worksheet. M. Silva, 11/25/98.

121 - 141, 142 & 145 185732, 185733 & 185736 "Acute Dietary Neurotoxicity Study with Methyl Parathion in Rats," (Weiler, M.S.; Covance Laboratories Inc., Madison, WI; Laboratory Study ID: Covance 6222-116; 4/30/99). Methyl parathion technical (99.6% pure) was fed in diet to 10 groups of Crl:CD® (SD) IGS BR (Sprague Dawley, *Rattus norvegicus*) rats (10/sex/dose, Groups 1 - 5 for neurotoxicity; 16/sex/dose, Groups 6 - 10 for "time-of-peak effect" on cholinesterase activity). Groups 1 and 6 received basal diet, while the other groups received 1, 1.5, 3 or 12 mg/kg in an acute, single dose. On days 1 and 15 at the time-of-peak-effect (0.5 - 1.5 hrs post-dosing & at study termination) 8/sex/dose (groups 5 - 10) were bled for RBC and plasma cholinesterase activity, brain histopathology and brain cholinesterase activity. Day 15 Groups 1 - 5 (8/sex/dose) were examined for neuropathology. NOEL (actual consumption) = 1.6 mg/kg (males) & 1.3 mg/kg (females) The females, targeted at 12 mg/kg (actual dose = 4.9 & 3.5 mg/kg in males and females, respectively), had slight ataxia and a negative air drop righting reflex on Day 1. A female at 12 mg/kg (3.7 mg/kg acutal dose) had a negative air drop righting reflex on Day 1. The mean number of rears in the open field was statistically significantly lower for the high-dose females on Day 1. Body temperatures of both sexes were statistically significantly lower than controls on Day 1 at the time-of-peak effect. Day 1 at time-of-peak effect, the mean 10-minute interval counts of the first two 10-minute intervals and the total counts (0-10, 10-20, 0-40 minutes) for the high-dose males and females were statistically significantly lower than controls. Animals at target dose 12 mg/kg had slightly decreased body weight at Day 1.) Not acceptable and not upgradeable (no positive control data, wide variation in achieved dose and in ChE inhibition versus dose.). No adverse effect. M. Silva, 4/19/02.

121 - 134 & 135 185725 & 185726 "5-Day Dermal Neurotoxicity Study with Methyl Parathion in Rats," (Weiler, M.S.; Cheminova Agro A/S, Harboøre, Denmark; Lab Study ID #: Covance 6222-115; 5/27/99; Pathology Report, 5/28/99). Methyl parathion 4E formulation (43.9% pure) was dermally administered on the shaved dorsal surface of Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (10/sex/dose--Main Group; 16/sex/dose ChE group) for 5 days (6-7 hours/day exposure, unoccluded) at 0, 1, 2 and 3 mg/kg/day. Systemic NOEL > 3 mg/kg (There were no treatment-related systemic effects at any dose.) Neurotoxicity NOEL = 2 mg/kg (There were 2 females at 3 mg/kg that had effects consistent with ChE inhibition (miosis and a negative pupillary response) on days 4 and 6. One male at 3 mg/kg had slight tremors on day 6.). ChE NOEL < 1 mg/kg (Males at 2 and 3 mg/kg on day 4 (20 & 19%, respectively) and females at 3 mg/kg on day 6 (41%) had statistically significantly decreased RBC ChE. Females on day 4 at 3 mg/kg had statistically significantly decreased frontal cortex ChE (52%). Females at 3 mg/kg had statistically significantly decreased plasma ChE on day 6 (36%). Striatum ChE in females at 1 and 3 mg/kg was

statistically significantly decreased (45 & 47%, respectively). Not a FIFRA Guideline study (unacceptable). Possible adverse effect (decreased brain ChE in females). M. Silva, 5/3/02

121 - 137 185728 "A 2-Week Range-Finding Dermal Toxicity Study of the Potential Effects of Methyl Parathion in Rats," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Lab Study ID #: 97501; 9/24/99). Methyl parathion formulation (47.5% pure) was dermally administered on the shaved dorsal surface of Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (5/sex/dose) for 2 weeks (5 days/week; 6 hours/day exposure, unoccluded) at 0 (formulation + xylene in place of Methyl parathion), 7, 15, 33, 75 and 150 mg/kg/day. Systemic NOEL = 15 mg/kg; equivalent to 7 mg/kg a.i. (There was decreased body weight and food consumption and increased mortality and clinical signs at $\geq$ 33 mg/kg in both sexes.) Neurotoxicity NOEL = 15 mg/kg; equivalent to 7 mg/kg a.i. (There was increased incidence in tremors and signs of neurotoxicity in both sexes at $\geq$ 33 mg/kg. There were increased effects in the FOB at $\geq$ 33 mg/kg.) ChE NOEL < 7 mg/kg; equivalent to 3 mg/kg a.i. (Blood, plasma and brain ChE were statistically significantly decreased at all doses (where there were sufficient numbers of animals to assess).) **Possible adverse effect: Increased neurotoxicity and blood and brain ChE inhibition.** Data are supplemental. Not a FIFRA Guideline study. M. Silva, 5/9/02.

121 - 139 & 140 185730 & 185731 "4-Week Dermal Toxicity Study of Methyl Parathion in Rats," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Lab Study ID #: 97533; Final report 4/27/01; Final Report Amendment, 5/25/01). Methyl parathion technical (96.5% pure) was dermally administered on the shaved dorsal surface of Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (42/sex/dose) for 4 weeks (5 days/week; 6 hours/day exposure, unoccluded) at 0 (0.5% carboxymethylcellulose/0.1% tween 80 in deionized H_2O), 0.3, 1.0, 2.2 and 5.0 mg/kg/day. Treatment was followed by a 4 week recovery period. Systemic NOEL = 2.2 mg/kg (There was increased mortality in both sexes at 5 mg/kg. Animals dying on study showed clinical signs (red fur staining on the muzzle, skin scab on the hindpaw; yellow fur staining at the lumbar region, dry tail). Hematocrit was statistically significantly decreased in females at 5 mg/kg on day 56. RBC size distribution width (RDW) was statistically significantly increased in females on day 56. Ophthalmology and dermal scores were negative.) Neurotoxicity NOEL = 0.3 mg/kg (There was increased incidence in tremors in females at 5 mg/kg (day 5) and in pinpoint pupils at $\geq$ 1.0 mg/kg on day 28.) ChE NOEL < 0.3 mg/kg (Blood ChE was statistically significantly decreased at $\geq$ 1.0 mg/kg in males and in all doses for females. Brain ChE was statistically significantly decreased at all doses in both sexes. After the 4-week recovery, brain ChE remained depressed at all dose levels.) Data are supplemental. Not a FIFRA Guideline study (No clinical chemistry other than ChE. There were no positive control data for the FOB included in the study.). M. Silva, 5/9/02.

121 - 138 185729 "A 13-Week Dermal Study of the Potential Effects of Methyl Parathion on Behavior, Neurochemistry, and Neuromorphology in Rats," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; 9/24/99). Methyl parathion formulation (47.5% pure) was administered dermally (unoccluded) to Crl:CD® (SD) IGS BR (Sprague Dawley, *Rattus norvegicus*) rats at 0 (vehicle = xylenes), 0 (untreated control), 2.5, 8.0 and 25 mg/kg/day (expressed as formulation) for 6 hours/day, 5 days/week, over 13 weeks, except weeks 4, 8 and 13 when main study animals were treated for 4 days, to accommmodate the schedule for behavioral evaluations. There were 14/sex/dose in the main study groups and another component was animals assessed for cholinesterase activity (24/sex/dose at 0 (vehicle control) and 25 mg/kg and 16/sex/dose at 0 (untreated), 2.5 and 8 mg/kg/day). A 3 month recovery observation followed the 13 week treatment. Systemic NOEL = 8 mg/kg (Two males and 2 females at 25 mg/kg (ChE phase) died or were

euthanized. Red/flaking skin was observed at the dosing site and there was incoordination. Erythema red/scabbed skin at the dosing site occurred in vehicle control and at 25 mg/kg.) Neurotoxicity NOEL = 8 mg/kg (Clinical signs for ChE phase animals dying/euthanized prior to study termination were tremors, decreased activity, dehydration, labored breathing, fur staining, tremors, thinness, reduced core temperature (cold to touch) and salivation at 25 mg/kg.) Behavioral NOEL > 25 mg/kg (There were no treatment-related effects to behavior at any dose.) ChE NOEL < 2.5 mg/kg (Plasma ChE was statistically significantly decreased in males at week 1 ($\geq$ 2.5 mg/kg), at week 5 ($\geq$ 8 mg/kg) and at week 14 (25 mg/kg) and in females at weeks 1 and 5 (25 mg/kg) and week 14 ($\geq$ 8 mg/kg). RBC ChE was statistically significantly reduced in males at weeks 1, 5 and 14 ($\geq$ 2,5 mg/kg) and in females at weeks 1 ($\geq$ 8 mg/kg) and weeks 5 and 14 ($\geq$ 2.5 mg/kg). ChE from all brain sections in both sexes were statistically significantly decreased at week 14 ($\geq$ 2.5 mg/kg) but there was less inhibition at week 1 (M: hippocampus $\geq$ 2.5 mg/kg; striatum $\geq$ 8 mg/kg; cerebral cortex 25 mg/kg; F: all sections $\geq$ 8 mg/kg).) Unacceptable, upgradeable (A positive control is required for FOB, according to FIFRA Guideline recommendations). M. Silva, 4/25/02.

METABOLISM

** 121 - 136 & 147 185727 & 185738 “A Study to Determine the Urinary Elimination of para-Nitrophenol and its Conjugates Following Dermal Exposure of Rats to Methyl Parathion,” (Sved, D.W.; Cheminova A/S, Lemvig, Denmark; Project ID #: WIL-157018; Final report 7/13/01). [^{14}C]-Methyl parathion (56.7 mCi/mmol; 98% pure) was dermally applied to a 10-cm^3 area of shaved skin of Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (5 males/dose; single dose) at 1.0 or 12 ug/cm^2 (equivalent to 0.04 & 0.46 mg/kg bwt or 24.6 & 276 uCi/ml) for 10 hours. 4-Nitrophenol (PNP), p-nitrophenyl sulfate potassium salt and p-nitrophenyl $-D-glucuronide were used as reference standards. Absorbed dose = 80% (approximately) of the applied dose (Group 1 = 74.4 - 92.4%, mean: 84.4%; Group 2 = 74 - 84.6%, mean: 79.4%). Group 1 skin retained 1.7% of the dose at the site and 2.0% of the dose in skin under the dose site appliance. Group 2 skin retained 2.6%at the site of dosing and 1.4% in skin under the dose site appliance. Almost all of the absorbed dose was eliminated in urine during the exposure period. Group 1 had 51 - 75% eliminated in the urine during the 10-hour exposure and Group 2 had 48 - 66% eliminated during this time period. At 72 hours, only 2 - 3% of the absorbed dose had not been eliminated (carcass retained radioactivity < 1%). After acid hydrolysis of urine, compounds related to PNP accounted for 89% of urinary radioactivity in Group 1 and 99% in Group 2. After acid hydrolysis of the urine, 67 - 92% of the radioactivity was an unidentidfied component (a transformation product of PNP and PNP conjugates produced as an artifact of the hydrolysis procedure). This did not affect the ability to calculate the % conversion of absorbed dose of methyl parathion to PNP and PNP conjugates. For Group 1 the average level of conversion was 86.2% and for group 2 the average level of conversion was 97.4%. The overall average level of conversion was 91.8%. At 96 hours all animals were terminated. Acceptable. No adverse effect. M. Silva, 5/14/02.

121 - 147 185738 “Methyl Parathion: Proposed Method for Calculating the Internal Dose Received from Measurement of p-Nitrophenol in Worker Exposure Urine Biomonitoring Studies,” (D. Allemang; Cheminova, Inc., Washington, DC; 8/16/01). This document was submitted to the USEPA as a proposal for calculating the internal dose received from measurement of p-nitrophonol (PNP) in the worker exposure urine biomonitoring studies that the Registrants are conducting with emulsifiable concentrate (EC) and Penncap-M® formulations of methyl parathion. The data are supplemental (no worksheet). M. Silva, 6/6/02

121 - 148 185739 “A Two Year Chronic Feeding Study of Methyl Parathion in Rats - Re-Evaluation of Neuropathology,” (O’Shaughnessy, D.; D. O’Shaughnessy Consulting, Inc., Sparta, NJ, 2/8/02). This volume contained (in addition to the re-evaluation of neuropathology), 8 references about neuropathology and evaluation of neuropathology in rats. The data are supplemental (no worksheet). M. Silva, 6/8/02